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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/108,673	07/01/1998	CHIN-LEOU TENG	ISIS-3105	2703

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	45

DATE MAILED: 12/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/108,673	TENG ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-27,44-50,53-55,57-64,66,67 and 79-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-27,44-50,53-55,57-64,66,67 and 79-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *41*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The application has been transferred to Examiner Quang Nguyen, Ph.D. in GAU 1636.

Applicants' amendment filed on 4/22/03 in Paper No. 44 has been entered.

Claims 25-27, 44-50, 53-55, 57-64, 66-67 and 79-91 are pending in the present application, and they are examined on the merits herein.

Following are new grounds of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-27, 66-82 and 89-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A method of delivering or enhancing penetration of an antisense nucleic acid across intestinal mucosa of a **non-human animal**, said method comprises **administering directly** to the intestinal mucosa with a composition comprising an antisense nucleic acid and at least one fatty acid, or pharmaceutically acceptable salt thereof, wherein said nucleic acid has a modified nucleobase, a modified sugar residue or a modified internucleosidic linkage; and

(2) A method of delivering a nucleic acid to the intestinal mucosa of a non-human animal, said method comprises **administering directly** to the intestinal mucosa with the composition of claim 83,

does not reasonably provide enablement for methods of delivering or enhancing penetration of an antisense nucleic or a nucleic acid across the alimentary canal of **a human**, and/or methods comprising the step of **contacting the alimentary canal by any route of delivery and/or at any site or portion of the alimentary canal** with a composition of the presently claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 25-27 are drawn to a method of enhancing penetration of an antisense nucleic acid across the alimentary canal of an animal comprising administering to said animal the composition of claim 44, wherein said composition enhances penetration of said nucleic acid across the alimentary canal of said animal, the same method wherein said administration is sublingual, endoscopic or rectal (claim 26) or oral (claim 27).

Claims 66-81 are drawn to a method of delivering an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a composition comprising a nucleic acid and at least two fatty acids, or pharmaceutically acceptable salts thereof, wherein said nucleic acid has a cytosine to 5-methyl-cytosine substitution; a 2'methoxyethoxy modification; a phosphorothioate linkage and a cytosine to 5-methyl-cytosine substitution; or a phosphorothioate linkage and a 2'-methoxyehtoxy modification. Claim 82 is drawn to a method of delivering an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a compound comprising a nucleic acid and capric acid or lauric acid or a pharmaceutically acceptable salt thereof, wherein said nucleic acid has a cytosine to 5-methyl-cytosine substitution or a 2'-methoxyethoxy modification.

Claims 89-90 are drawn to a method of enhancing penetration of an antisense nucleic acid across the alimentary canal of an animal comprising administering to said animal the composition of claim 83, wherein said composition enhances penetration of said nucleic acid across the alimentary canal of said animal, the same method wherein said administration is oral.

Claim 91 is directed to a method of delivering a nucleic acid to the instestinal mucosa comprising contacting the alimentary canal with the composition of claim 83.

The instant specification teaches by exemplification showing the preparation of formulations comprising oligonucleotides and fatty acids (caprate and laurate), and that the formulations have bioavailability after jejunal or colonic instillation in rats and dogs (see examples 11-14).

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the reasons discussed below.

(1) The breadth of the claims. With respect to claims 25-27, 66-81 and 88-90, they are drawn to a method of delivering or enhancing penetration of any antisense nucleic acid across the alimentary canal of any animal, including human, by administering to said animal or contacting the alimentary canal of said animal a composition of the present invention by any means of delivery at any part or portion of the alimentary canal (e.g., sublingual, endoscopic, rectal or oral). Claim 91 encompasses a method of delivering any nucleic acid, not necessarily limited to an antisense nucleic acid, to the intestinal mucosa by contacting the alimentary canal with a composition of the present invention by any routes of delivery. It is further noted that when read in light of the specification, the sole purpose for the methods as claimed in a human (encompassing with the scope of an animal) is to attain therapeutic effects (see instant specification, page 3, lines 21-27 and page 33, lines 28-30).

(2) The state and the unpredictability of the art. An embodiment of the instant claims (e.g., particularly for methods of enhancing penetration of any antisense nucleic acid across the alimentary canal of a human, and a method of delivering a nucleic acid to the intestinal mucosa of a human) falls within the realm of antisense therapy and gene therapy (claim 83). At the effective filing date of the present application, the attainment of any therapeutic effect via an antisense therapy was known to be highly unpredictable as evidenced by the teachings of Branch (TIBS 23:45-

50,1998; already of record), Rojanasakul (Advanced Drug Delivery Reviews 18:115-131, 1996; already of record) and Stull et al. (Pharmaceutical research 12:465-483, 1995; already of record). Branch stated "Antisense molecules and ribozymes capture the imagination with their promise of rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven. Furthermore, a wide variety of unexpected non-antisense effects have come to light" (see abstract). Branch further noted that although some of the unexpected non-antisense effects have clinical value, they are currently not predictable and rules for rational design can not be applied to the production of non-antisense drugs and that they must be explored on a case-by-case basis (page 50, col. 1).

Rojanasakul noted several problems associated with a successful *in vivo* use of antisense oligonucleotides, including the poorly uptake by cells due to their large molecular size and charge, hurdles associated with cellular targeting, affinity of the oligonucleotides to the target sites as well as their potential toxicity (see the entire document, especially the concluding remarks). Rojanasakul stated "The next challenge to antisense technology is in its application in humans. Like any other new technology, the development of the antisense concept is still faced with several obstacles. Nonetheless, **there is good reason for enthusiastic hope**" (page 126, col. 1, last paragraph).

Even several years after the effective filing date of the present application, Tamm et al. (The Lancet 358:489-497, 2001; already of record) still stated "There is **a**

potential role for antisense oligonucleotide in the treatment of disease", "One antisense drug has been approved for local treatment of cytomegalovirus-induced retinitis, and several antisense oligonucleotides are in clinical trials" and "Antisense oligonucleotides are well tolerated and **might have therapeutic activity**" (see abstract).

Additionally, at about the effective filing date of the present application, gene therapy in general was an immature and highly unpredictable art. This is supported by the report of Orkin et al. (Report and recommendations of the panel to assess the NIH investment in Research on gene therapy, pages 1-20, 1995) to the Director of NIH on the status of gene therapy. The report states "While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA advisory Committee (RAC)-approved protocols", and "Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and "Interpretation of the results of many gene therapy protocols has been hindered by a very low frequency of gene transfer, reliance on qualitative rather than quantitative assessments of gene transfer and expression, lack of suitable controls, and lack of rigorously defined biochemical or disease endpoints" (See pages 1-2 of the report). Even many years after the effective filing date of the present application, Dang et al. (Clin. Cancer Res. 5:471-474, 1999) still state "This workshop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the

development of molecular targets and stressed that all of these fields will need further advancement to make gene therapy a reality" (page 471, col. 1, last sentence of first paragraph). It has been noted that there are several factors limiting an effective gene therapy, and these include sub-optimal vectors, a lack of a stable *in vivo* transgene expression, and an efficient gene delivery to target tissues or cells.

Thus, it is clear that the attainment of any therapeutic effect via either antisense therapy or gene therapy was highly unpredictable at the effective filing date of the present application.

(3) The amount of direction or guidance presented. Apart from the exemplification showing the preparation of formulations comprising oligonucleotides and fatty acids or their salts (e.g., caprate and laurate), and that the formulations have bioavailability after jejunal or colonic instillation in rats and dogs (see examples 11-14), the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain *in vivo* bioavailability for the formulations of the present invention by any route of delivery at any part or portion of an alimentary tract in an animal, particularly by a sublingual or an oral delivery. It should be noted the bioavailability of an antisense nucleic acid or a nucleic acid in the formulations, particularly to any targeted cell or tissue *in vivo*, is variable depending on which route of delivery and at which part or portion of the alimentary tract. For example, it is entirely unclear how any antisense nucleic acid or any nucleic acid even in the presence of fatty acids can withstand the adverse acid environment of a stomach (part of the alimentary tract) without subjected to degradation or inactivation, and it is still being delivered to targeted cells or tissues at

an effective amount for attaining the desired results including the therapeutic effects contemplated by Applicants. It should be noted that the physiological art is recognized as unpredictable (MPEP 2164.03). Furthermore, there is no evidence of record that any therapeutic effects has been achieved or attained by a method as claimed by any composition of the present invention. The simple radioactivity measurements for oligonucleotide content in plasma and tissue samples are not deemed to be reasonable correlated to any therapeutic effects contemplated by Applicants, particularly in light of the state and the unpredictability of the relevant arts already discussed above.

Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present application to do so. Without sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed. Moreover, the Appeal courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel*.).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues raised above, the unpredictability of the gene therapy art as well as the physiological art in general, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 4/22/03 (pages 9-15) have been fully considered, but they are not found persuasive.

(1) With respect to the issue of attaining therapeutic effects, Applicants argue that the references cited by Examiner, including the teachings of Branch et al. and Stull et al., are insufficient to represent the broad area of antisense technology as unpredictable and do not reflect the state of the art as a whole at the time of filing. Applicants submitted selected chapters form a book entitled Antisense Drug Technology (Marcel Dekker, Inc., (2001)) as evidenced of the predictable state of the art of antisense technology. Applicants further argue that Whitesell (Antisense Research and Development 1:343-350, 1991) successfully performed *in vivo* modulation of N-myc expression in mice, Mirabelli et al. (Anti-Cancer Drug Design 6:647-661, 1991) notes that "the therapeutic indexes of phosphorothioate oligonucleotides appear to be quite high" and that "certain phosphorothioates ....are extremely well tolerated in animals", and Crooke (Annu. Rev. Pharmacol. Toxicol. 32:329-376, 1992) provides evidence that those skilled in the art were conducting pharmacokinetic data in mice and rats. Furthermore, Cossum et al. (The journal of Pharmacology and Experimental Therapeutics 267:1181-1190, 1993) discusses non-antisense effects and ways to avoid them *in vivo* by not using doses that are significantly greater than the antisense effective dose, indicating that by 1993, those skilled in the art were delivering antisense oligonucelotides *in vivo* where the only carrier was a phosphate buffer. Applicants further argue that a handful of oligonucleotide antisense molecules have been

successfully completed phase III trials and been FDA approved, and many other oligonucleotide antisense drugs are currently involved in clinical trials (Tamm et al., Lancet 358:489-497, 2001).

Upon reviewing the aforementioned articles cited by Applicants, none of the articles teaches that the attainment of therapeutic effects via antisense therapy as asserted by Applicants. The book chapters are drawn to methods of selecting sites in RNA for antisense targeting, suborgan phamacokinetics, and pharmacokinetic properties in humans as well as studies conducting pharmacokinetic in mice and rates, discussions on ways to avoid non-antisense effects, statements such as "the therapeutic indexes of phosphorothioate oligonucleotides **appear to be quite high**" and that "certain phosphorothioates ....**are extremely well tolerated in animals**" do not indicate that the attainment of therapeutic effects via antisense therapy was routine at the effective filing date of the present application. This is supported by numerous review articles including the teachings of Branch, Rojanasakul and Stull et al. already discussed above.

Even several years after the effective filing date of the present application, Tamm et al. (The Lancet 358:489-497, 2001) still stated "There is **a potential role for antisense oligonucleotide in the treatment of disease**", "One antisense drug has been approved for local treatment of cytomegalovirus-induced retinitis, and several antisense oligonucleotides are in clinical trials" and "Antisense oligonucleotides are well tolerated and **might have therapeutic activity**" (see abstract), let alone at the effective filing date of the present application. It is further noted that although several antisense

oligonucleotides are in clinical trials as noted by Tamm et al., this does not indicate that these antisense oligonucleotides can produce therapeutic effects. Furthermore, the results reported by Whitesell et al. do not reasonable correlate with the therapeutic effects contemplated by Applicants for the methods as claimed, because those results are generated by *in vivo* perfusion of unmodified N-myc antisense oligonucleotides in athymic mice with subcutaneous human neuroectodermal tumor xenografts, and do not involve the delivery of a composition of the present invention across an alimentary canal.

(2) With respect to the various references cited by Applicants and of record, Applicants argue that the references show both the successful enhancement of oligonucleotide penetration across the alimentary canal and treatment of an animal, demonstrating that methods of treatment using antisense molecules were routine in the art at the time of filing, and therefore, no undue experimentation is needed to practice the invention.

Examiner notes that all the previously cited references relate to the administration of antisense oligonucleotides via the blood stream or local administration in nude or SCID mice, and not through the alimentary canal as presently claimed. Contrary to Applicants' assertion that methods of treatment using antisense molecules were routine in the art at the time of filing, the reviews of Branch, Rojanasakul, Stull et al. and, Tamm et al. indicated otherwise as already discussed above.

(3) With respect to the Declaration of Dr. Mark K. Wedel, Applicants argue that the Declaration shows predictability of antisense technology and enablement of the claims. Applicants further argue that the absence of formulation details is not relevant to the purposes of the declaration, and that the data provided in Exhibits D, E, and F indicate the predictability of antisense technology and enablement of the claims.

The data provided in the Declaration appear to be produced by a different composition (e.g., absence of at least two fatty acids or pharmaceutically acceptable salt thereof) and by a different method (it is unclear from the Declaration whether the composition is delivered across the alimentary canal of an animal). Therefore, the results do not reasonably correlate with any therapeutic effects contemplated by Applicants for the present methods as claimed.

Accordingly, claims 25-27, 66-82 and 89-91 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-27, 66-82 and 89-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 25 and its dependent claims, there is no connection between the step of administering to an animal the composition of claim 44 which is directed to a composition comprising a nucleic acid and at least two fatty acids or pharmaceutically

acceptable salts thereof with enhanced penetration of an anti-sense nucleic acid across the alimentary canal of an animal recited in the preamble of the claimed method. Clarification is requested because the metes and bounds of the claims are not clearly determined.

In claims 66, 82 and dependent claims, there is no connection between the step of contacting an alimentary canal with a composition or a compound comprising a nucleic acid with the delivery of an anti-sense nucleic acid to the intestinal mucosa recited in the preamble of the claimed method. Additionally, it is unclear what is encompassed by the terms "the intestinal mucosa" and "the alimentary canal". Which intestinal mucosa and which alimentary canal do Applicants refer to? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Similarly, in claim 89 and its dependent claims, there is no connection between the step of administering to an animal the composition comprising a nucleic acid with enhancing penetration of an anti-sense nucleic acid across the alimentary canal of an animal recited in the preamble of the claimed method. Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 61-64, 82-89 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (WO 97/05903; Cited previously) in view of Dean et al. (U.S. 5,948,898; Cited previously).

With respect to the scope of enablement, Watts et al. disclose a composition for colonic delivery comprising a polar drug (including genes such as DNA or DNA constructs and antisense agents, see page 8, lines 11-12) and an absorption promoter which comprises a mixture of a fatty acid having 6 to 16 carbon atoms (e.g., capric acid, see abstract, page 5, lines 18-20) or a salt thereof and a dispersing agent, and a method for delivering the composition to the proximal colon in an animal by a means (with a coating material) that prevents release of the polar drug and absorption promoter until the formulation reaches the colon (page 13, line 30 continues to line 11 of page 14, page 9 line 26 continues to line 16 of page 13).

Watts et al. do not specifically teach that DNA or DNA constructs or antisense agents have a modified nucleobase (specifically 5-methyl-cytosine substitution) or a

modified sugar residue (2'-methoxyethoxy modification) or that the antisense agents decrease the expression of a cellular adhesion protein or the rate of cellular proliferation.

However, at the effective filing date of the present application Dean et al. already teach antisense oligonucleotides containing a methoxyethoxy modification at the 2' position of at least one nucleotide, that inhibit protein kinase C expression (see abstract and col. 3, lines 24-45) whose overexpression is correlated with increased tumorigenicity in cultured cells inoculated into nude mice (col. 1, line 60 continues to line 7 of col. 2). Dean et al. also teach that the oligonucleotides can be used in diagnostics as well as research reagents (col. 7, lines 26-28), and that the oligonucleotides can be administered topically (e.g., vaginally, rectally or orally, see col. 8, lines 45-59). Dean et al. further teach that there is a desire in the art to inhibit specific PKC isozymes both as a research tool and in diagnosis and treatment of diseases which may be associated with particular isozymes (line 66 of col. 2 continues to line 2 of col. 3).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the composition or method taught by Watts et al. by utilizing the antisense oligonucleotides specific for nucleic acids encoding protein kinase C taught by Dean et al. to establish a research tool (e.g., an animal model) to study the effects of the PKC antisense-oligonucleotides.

One of ordinary skilled artisan would have been motivated to carry out the above modification because Dean et al. clearly teach that the methoxyethoxy modification at the 2' position of the sugar moiety of at least one nucleotide increases both affinity of

the antisense oligonucleotide for its target and nuclease resistance of the oligonucleotide (col. 6, lines 22-27). Additionally, Dean et al. further teach that there is a desire in the art to inhibit specific PKC isozymes both as a research tool and in diagnosis and treatment of diseases which may be associated with particular isozymes (line 66 of col. 2 continues to line 2 of col. 3).

One would have a reasonable expectation of success to carry out the presently claimed invention in light of the teachings of Watts et al. and Dean et al., coupled with a high level of skills of an ordinary skilled artisan in the art at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339 or (571) 272-0776 after 01/13/2004.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

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